Original Article

Electrochemical skin conductance to assess peripheral neuropathy in rheumatic diseases with or without type 2 diabetes using sudoscan

Osama M. I. Mohamed[1,2], Nagwa M. M. Ali[3], Mohammed O. Ibrahim[4], Dana Sarmini[5], Farah Ibrahim[6], Mariam Al Hosany[1]

[1]Ambulatory Healthcare Services, SEHA, Pure Health, Abu Dhabi, UAE, [2]College of Medicine, Khalifa University, Abu Dhabi, UAE, [3]Rheumatology, Mediclinic Airport Road Hospital, Abu Dhabi, UAE, [4]College of Medicine, Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai, UAE, [5]Department of Pediatrics, Al Jalila Children's Hospital, Dubai, UAE, [6]College of Medicine, Gulf Medical University, Ajman, UAE

Abstract

Introduction: Peripheral neuropathy (PN) occurs in diabetes mellitus. However, the association between PN and rheumatic disease (RD) has not been fully investigated. The aim of this study was to assess the prevalence of PN in patients with RDs with or without Diabetes Mellitus. **Methods:** A Cross-sectional cohort study, data extracted from patients medical records started in September 2023 to January 2024 in Abu Dhabi, UAE. A Sudoscan machine report was used to assess The electrochemical skin conductance (ESC), Sudomotor dysfunction is evaluated according to the ESC measured on the feet: >60 μS = no dysfunction; 60–40 μS = moderate dysfunction; and <40 μS = severe dysfunction. **Results:** Eighty-one patients with RDs, mean age 58 ± 12. There were 55 females (67.9%), and 26 males (32.1%) attended an ambulatory healthcare clinic in Abu Dhabi, UAE. Thirty-three (40.7%) had diabetes, while 48 (59.3%) did not have diabetes. The mean glycated haemoglobin A1c (HBA1c) was 7.4% in diabetic patients and 5.8% in non-diabetic patients Additionally, all patients had a mean blood pressure of 134/72 and a mean Body Mass Index (BMI) of 31.40 kg/m^2. Among the study patients, the most common RD was osteoarthritis, which affected 56.8% of the patients. The smallest percentage of patients with PN was found in those with IgG4, at 1.2%. The prevalence of Sudomotor dysfunction (ESC feet: <60 μS) was 72.8% in patients with RDs (all patients diabetic and non-diabetic), while the prevalence of sudomotor dysfunction (ESC feet: <60 μS) in RDs patients with diabetes was 75.8% and 70.8% in RDs patients without diabetes, there was no significant difference between in prevalence of sudomotor dysfunction in RD patients with diabetes compared to RD patients without Diabetes. **Conclusion:** Sudomotor dysfunction appears to be common among patients with RD regardless they have diabetes or not. This study recommends screening all RD patients for Sudomotor Dysfunction.

Keywords: Diabetes, neuropathy, rheumatic diseases, screening, sudomotor dysfunction, sudoscan

Introduction

Rheumatic diseases (RD) are chronic inflammatory autoimmune diseases induced by antibodies or T-cell responses directed against self-antigens, which can affect all body systems, including the central nervous system (CNS) and peripheral nervous system (PNS).[1]

When the PNS is involved in RD, peripheral neuropathy (PN) is the most common complication, which comprises a heterogeneous group of disorders, such as mononeuropathy, polyneuropathy, and mononeuritis multiplex. PN may be a manifestation or a

Address for correspondence: Dr. Osama M. I. Mohamed, Ambulatory Healthcare Services, SEHA, Pure Health, Abu Dhabi, UAE.
E-mail: drosama7878@gmail.com

Received: 06-07-2024 **Revised:** 14-08-2024
Accepted: 23-08-2024 **Published:** 13-01-2025

Access this article online

Quick Response Code:

Website: http://journals.lww.com/JFMPC

DOI: 10.4103/jfmpc.jfmpc_1171_24

How to cite this article: Mohamed OM, Ali NM, Ibrahim MO, Sarmini D, Ibrahim F, Al Hosany M. Electrochemical skin conductance to assess peripheral neuropathy in rheumatic diseases with or without type 2 diabetes using sudoscan. J Family Med Prim Care 2025;14:226-31.

characteristic sign of immune system dysfunction, with variable prevalence and prognosis in RD. Therefore, rapid recognition and treatment are essential. However, because of a varied, complex spectrum of overlapping clinical manifestations, PN is an underdiagnosed complication in RD and a particular challenge for rheumatologists and neurologists. Glucocorticoids and immunosuppressants are usually administered as basic and routine treatments of PN in RD.[2]

However, as reported in experimental models of neuropathic pain, glucocorticoids may cause hyperalgesia, exacerbate neuropathic pain, trigger the early phase of pain induction, and indeed produce hyperalgesia.[3]

A possible strategy to find an effective treatment for PN is shifting the focus to new biological targets and relevant molecular events in the PNS; in particular, neuroactive steroids are a highly promising therapeutic option as these steroids can modulate PNS functions.[4]

The prevalence of diabetic PN (DPN) varies according to different authors and instruments used for diagnosis; it was estimated to be between 16% and 87%.[5-7] At the time of diagnosis of type 2 diabetes, mellitus (T2DM) 7.5% of patients already have neuropathy.[8]

Sudoscan is an FDA-approved device that uses reverse iontophoresis and chronoamperometry to evaluate sweat gland function based on sweat chloride concentrations. The body's sweat glands are linked to the autonomic nervous system via sympathetic C fibers. These fibers are long, thin, unmyelinated, or thinly myelinated. Due to their characteristics, sweat gland nerve function can be a surrogate for small-caliber sensory nerve damage in neuropathy. In addition, as autonomic nerve fibers recover quicker than sensory nerve fibers, sudomotor function testing could be used as an early indicator of treatment efficacy in neuropathy.[9]

Sudoscan consists of two sets of electrodes for the hands and feet connected to the computer for recording and data management. The subject places the palms of the hands and the soles of the feet on the electrodes. This test requires 2 min, during which four combinations of 15 different low voltage DC are applied. The device generates a current between the anode and cathode proportional to chloride concentration via reverse iontophoresis, producing a voltage at the cathode with an intensity of around 0.2 mA. No subject preparation is required for this test.[10]

The machine measures electrochemical skin conductance (ESC), the ratio of the current measured over the constant power applied expressed in micro-Siemens (μS) for the hands and the feet (right and left sides). ESC expressed in micro-Siemens (μS), is the ratio between the current generated and the constant DC stimulus (≤4 V) applied to the electrodes. Sudomotor dysfunction is evaluated according to the ESC measured on the feet: >60 μS = no dysfunction; 60–40 μS = moderate dysfunction, and <40 μS = severe dysfunction.[11]

Sudoscan is a sensitive tool to detect neuropathy in patients with diabetes. The value of Sudoscan in diagnosis and follow-up of neuropathy is well established.[12] However, the use of Sudoscan tp detect neuropathy in RD is less well studied. This study aimed at assessing the prevalence of PN among patients with RDs using sudomotor function testing and comparing the prevalence of PN among RD patients with and without type 2 diabetes using sudomotor function testing.

Materials and Methods

Study design, setting and participants

This was a cross-sectional cohort study, which included 81 patients (55 female and 26 male adults), extracted from the electronic medical records, who attended a public Ambulatory Healthcare Services center from September 2023 to January 2024 in Abu Dhabi, UAE. Ethical approval was granted by the Ambulatory Healthcare Services Human Research Committee.

Sampling

The following equation was used to calculate the sample size of patients in this cross-sectional study.[13]

$$\text{Sample size} = \frac{z_{1-\alpha/2}^{\ 2}\ p(1-p)}{d^2}$$

$z_{1-a/2}$ = Is standard normal variate at 5% type 1 error ($P < 0.05$) it is 1.96. *P* values are considered significant below 0.05 in this study

p = Expected proportion of PN among patients with RD based on previous studies was 5.6%.[14]

d = sample size with the precision/absolute error of 5% at type 1 error of 5%

According to the above formula, sample size 81 patients who attended an Ambulatory Healthcare Center were included to complete the required sample size.

$$\textit{Sample size} = \frac{(1.96X1.96)\,X\,0.056(1-0.056)}{0.05X0.05} = 81$$

Inclusion criteria

- Adults above the age of 18 years old.
- Patients with documented RDs diagnosis were only included.

Assessment

- Patients' age, gender, weight, height, blood pressure, HbA1c level, and the documented diagnosis of RD and diabetes were extracted from the electronic medical records.
- The patient was considered diabetic if HbA1c was 6.5 or more.

Peripheral sympathetic autonomic function was assessed by reviewing the patients Sudoscan report, which was attached to the patient's medical record, (Impeto Medical, Paris, France) through the measurement of ESC of hands and feet.

- The mean of left and right readings of both hands and feet was used for the analysis. Sudomotor dysfunction was evaluated according to the ESC measured on both hands and feet: >60 µS = no dysfunction; 60–40 µS = moderate dysfunction; and < 40 µS = high dysfunction 11.[15] For this analysis, we classified the population into two groups: those with or without Sudoscan alteration (ESC ≤ 60) in feet.

Statistical analysis

Data were entered in a Microsoft Excel spreadsheet and were analyzed using Statistical Product and Services Solutions (SPSS) 24.0.[16] For all comparisons, the significance level for rejecting the null hypothesis was $P < 0.05$. Results are presented as mean ± standard deviation (SD). The following statistical methods were applied: descriptive analysis, variation analysis, student's *t*-test for two independent samples, and Chi-square test of independence to determine whether there is an association between categorical variables.

Results

Eighty-one patients with RDs and diabetes, mean age 58 ± 12, 55 females (67.9%), and 26 males (32.1%), participated in this study. In terms of biomedical parameters, all participants showed controlled blood pressure (134/72), the mean BMI was (31.40), 33 (40.7%) Patients with DM, and 48 (59.3%) Patients without DM, there was a significantly higher proportion of non-diabetic patients compared to diabetics as presented in Table 1.

Regarding the distribution of RDs, osteoarthritis (OA) was the most common RD among study patients, with a percentage of 57%. In contrast, the smallest number was IgG4 with the percentage of 1.%, as shown in detail in Figure 1.

There was a significantly higher proportion of RD patients diagnosed without DM compared to RD patients with DM, the *P* value was <0.05 as shown in Figure 2.

Table 2 shows the frequency distribution of RDs in patients with and without diabetes. There was a significantly higher proportion of OA patients without Diabetes compared to OA patients with Diabetes. There was no significant difference in other RD patients with RDs with or without diabetes.

The mean HbAb1c among people with diabetes was 7.4 and the mean HbA1c among non-diabetics was 5.8, there was a statistically significant higher mean HbA1c in level among diabetics as presented in Table 3.

There was a significantly higher proportion of patients with RD having ESC dysfunction (neuropathy) among the study population compared to patients with normal ESC as shown in Figure 3.

Frequency distribution of ESC dysfunction (PN) among all RD patients (all participants), a RD with DM, and RD without DM were 72.8%, 75.8%, and 70.8% respectively. PN prevalence was nearly similar among all groups without a statistically significant difference in RD with DM compared to RD without DM.as shown in Figure 4.

There was a significantly higher proration among RD patients with and without diabetes having ESC dysfunction as shown in Table 4, the prevalence of neuropathy was significantly high in both groups regardless presence and absence of diabetes.

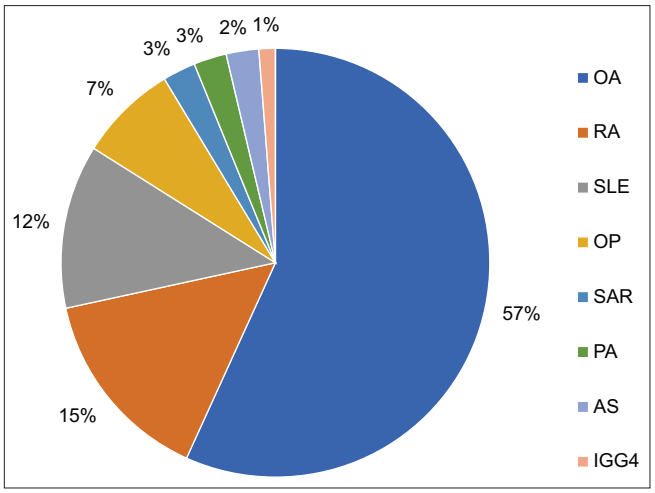

Figure 1: Frequency distribution of rheumatic diseases among participants. OA Osteoarthritis, RA Rheumatoid Arthritis, SLE Systemic lupus Erythematosus, OP Osteoporosis, SAR Sarcoidosis PA Psoriatic Arthritis, AS Ankylosing Spondylitis, IGG4. IGG4 Disease

Table 1: Demographic characteristics of included patients

	All patients *n*=81
Mean age (years)	58±12
Gender	
Female	55 (67.9%)
Male	26 (32.1%)
Mean BMI	31.40
Mean Blood Pressure	134/72
Mean HbA1c*	
Patients with DM *n*=33 (40.7%)	7.40±1.10
Patients without DM *n*=48 (59.3%)	5.81±0.26

*P<0.05 Patients with DM versus Patients without DM

Table 2: Frequency distribution of rheumatic diseases among patients with or without diabetes

Rheumatic Diseases	Patients with Diabetes		Patients without Diabetes	
	Number	%	Number	%
OA	17*	(37%)	29*	(63%)
RA	5	(41.6%)	7	(58.4%)
SLE	5	(50%)	5	(50%)
OP	3	(50%)	3	(50%)
PSA	1	(50%)	1	(50%)
AS	1	(50%)	1	(50%)
Sarcoidosis	1	(50%)	1	(50%)
IgG4	0	(0%)	1	(100%)
Total	33	(40.7%)	48	(59.3%)

*P<0.05 Patients with DM versus Patients without DM. OA Osteoarthritis, RA Rheumatoid Arthritis, SLE Systemic lupus Erythematosus, OP Osteoporosis, SAR Sarcoidosis PA Psoriatic Arthritis, AS Ankylosing Spondylitis, IGG4. IGG4 Disease

Table 3: Mean HbA1c among patient with rhematic diseases without diabetes

A1c Level	*n* (%)	Minimum	Maximum	Mean±SD	*P*
Participants with DM A1c ≥6.5%	33 (40.7%)	6.5	10.5	7.40±1.10	<0.05
Participants without DM A1c <6.5%	48 (59.3%)	5.0	6.3	5.81±0.26	CI 95% (1.26-1.92)

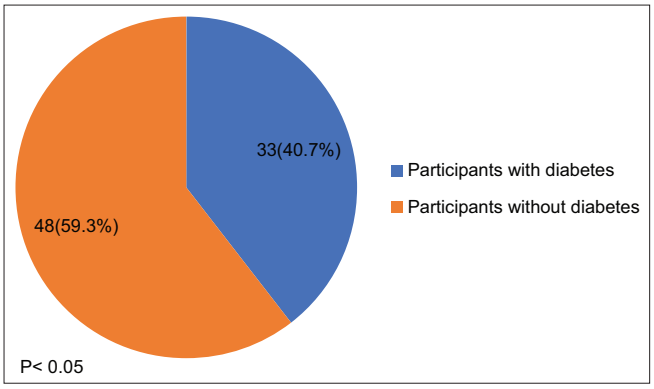

Figure 2: Frequency distribution of diabetes among patients with rheumatic diseases

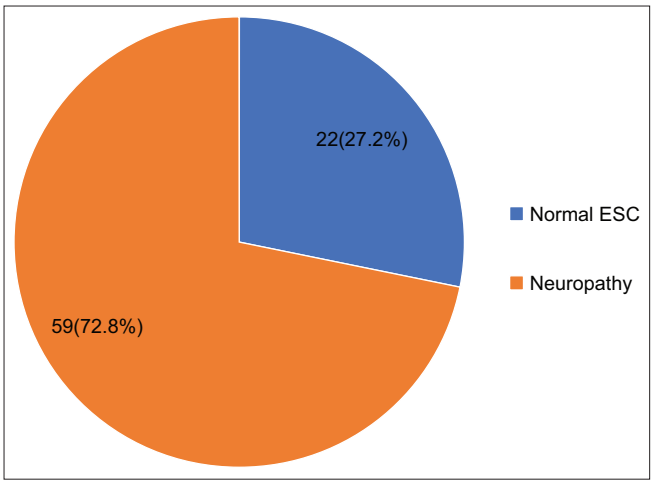

Figure 3: Frequency distribution of peripheral neuropathy among patients with rheumatic diseases (all participants). *P* = 0.0000, ESC < 60 µS = normal; ESC > 60 µS = dysfunction (Neuropathy). ESC: Electrochemical Skin Conductance

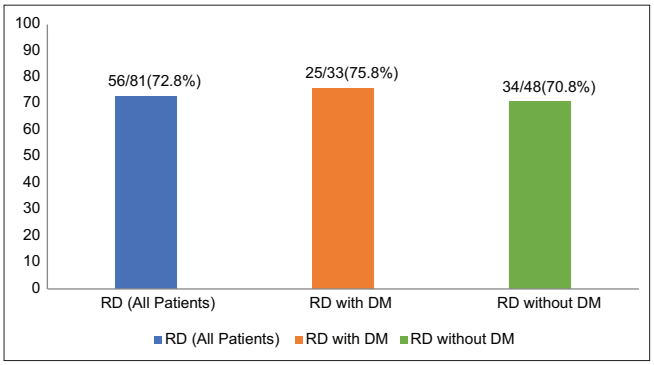

Figure 4: Frequency distribution of ESC dysfunction among all rheumatic disease patients, rheumatic disease patients with DM, and RD without DM. P > 0.05 versus RD with DM and RD without DM, ESC < 60 µS = normal; ESC > 60 µS = dysfunction (Peripheral Neuropathy) ESC: Electrochemical Skin Conductance

Frequency of neuropathy among RD patients, 100% of patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS), sarcoidosis, and IgG4 were affected by neuropathy while 69.6 of patients with OA were affected by neuropathy as shown in Table 5.

There was statistically significant higher mean ESC dysfunction in hands and feet among patients with RD compared to patients with normal ESC, as shown in Table 6.

Discussion

This study included 81 patients with RDs and DM, 55 females (67.9%) and 26 males (32.1%). The number of patients with DM was 33, and the number of patients without DM was 48. There was a significant higher proportion of RD patient diagnosed without DM compared to RD patients with DM, *P* value was <0.05, and the mean HbA1c of patients with DM was 7.40 ± 1.10%. Regarding biomedical parameters, all participants showed controlled blood pressure, but the mean BMI was above 30 kg/m^2 with obesity. Regarding the distribution of RDs, OA was the most common RD among study patients, with a percentage of 56.8%. In contrast, the smallest number was IgG4, with a percentage of 1.2%.

Prevalence of Sudomotor dysfunction (ESC feet: <60 µS) was 72.8% in patients with RDs (all patients diabetic and non-diabetic), while the prevalence of sudomotor dysfunction (ESC feet: <60 µS) in RDs patients with diabetes was 75.8% and 70.8%in RDs patients without diabetes. ESC dysfunction (Autonomic neuropathy) among patients with different RDs was 69.6%, 83.3%, 75%, 80%, 0%, 100%, 100%, 100%, 72.8% in OA, OP, RA, SLE, PsA, AS, IgG4, and Sarcoidosis, respectively.

In this study, ESC dysfunction (Autonomic neuropathy), prevalence among patients with RD and diabetes was 75.8%. The prevalence of diabetic PN among patients with RDs varies according to different authors and instruments used for diagnosis; it is estimated to be between 16 and 87% in many studies.[14] The results of this study are consistent with a study conducted by Kaely *et al.* 2019, they found 75.28% of patients with RA had PN electro physiologically, whereas 20.89% had superficial touch sensory loss on examination.[17] The results of this study are also consistent with a study conducted in the USA, about 60% to 70% of people with diabetes have mild to severe forms of nervous system damage. The results of such damage include impaired sensation or pain in the feet or hands, slowed digestion of food in the stomach, carpal tunnel syndrome, erectile dysfunction, or other nerve problems.[15]

Table 4: Normal and ESC Dysfunction among patients with rheumatic diseases with and without diabetes

Diabetes	ESC	*n* (%)	*P*
Yes	Normal ESC	8 (24.2%)	0.03
	ESC dysfunction	25 (75.8%)	
	Total	33 (100.0%)	
No	Normal ESC	14 (29.2%)	0.04
	ESC dysfunction	34 (70.8%)	
	Total	48 (100.0%)	

ESC <60 µS=normal; ESC >60 µS=dysfunction ESC: Electrochemical Skin Conductance

Table 5: Frequency distribution of ESC among patients with rheumatic diseases

Rheumatic diseases	Electrochemical Skin Conductance (ESC)		Total
	Normal ESC *n* (%)	ESC Dysfunction *n* (%)	
Osteoarthritis	14 (30.4%)	32 (69.6%)*	46 (100.0%)
Osteoporosis	1 (16.7%)	5 (83.3%)*	6 (100.0%)
Rheumatoid Arthritis	3 (25.0%)	9 (75.0%)*	12 (100.0%)
Systemic Lupus Erythematosus	2 (20.0%)	8 (80.0%)*	10 (100.0%)
Psoriatic Arthritis	2 (100.0%)	0 (0%)	2 (100.0%)
Ankylosing Spondylitis	0 (0%)	2 (100.0%)	2 (100.0%)
IgG4	0 (0%)	1 (100.0%)	1 (100.0%)
Sarcoidosis	0 (0%)	2 (100.0%)	2 (100.0%)

*P<0.05 patient with normal ESC versus dysfunction ESC. ESC: Electrochemical Skin Conductance ESC <60 µS=normal, ESC >60 µS=dysfunction

Table 6: Mean ESC in hand and feet among patients with rheumatic diseases

ESC among RD	*n* (%)	Mean (SD)	*P*
Mean ESC Hand			
Normal ESC	22 (27.16%)	72±14	<0.05
ESC Dysfunction	59 (72.84%)	51±18	
Mean ESC Feet			
Normal	22 (27.16%)	75±7	<0.05
ESC Dysfunction	59 (72.84%)	58±17	

ESC: Electrochemical Skin Conductance ESC <60 µS=normal, ESC >60 µS=dysfunction

In this study, the prevalence of autonomic neuropathy among OA patients was 64%. In a systematic review and meta-analysis, neuropathic pain prevalence in people with knee or hip OA is considerable at 44%–84.6%.[18] The reason for the higher prevalence of neuropathy in this study may be due to other potential causes of neuropathic pain, like DM. There were 13 (28.26%) patients diagnosed with DM with OA.

OA may lead to neuropathy using chronic pressure. A study by Kawanishi *et al.*[19] demonstrated that background morphologic changes in the cubital tunnel during elbow motion in patients with elbow OA had been examined in cubital tunnel morphology during elbow motion and characteristics of medial osteophyte development to elucidate whether cubital tunnel area and medial osteophyte size are factors contributing to cubital tunnel syndrome in patients with elbow OA, this study concluded that the effect of medial osteophytes on the ulnar nerve, especially on the humeral side, rather than narrowing of the cubital tunnel, may be a causative factor for cubital tunnel syndrome with elbow OA. A study by Garip *et al.* demonstrated that the prevalence of neuropathic pain was 44% in OA compared with control patients; prevalence was higher in OA [Odds ratio = 12.46 95% confidence interval (3.89–39.85)] (P = 0.00).[20] Sensory neuropathy in patients with hand OA may be caused by the radial nerve's superficial branch involvement. superficial radial neuropathy was detected in 68.8% of the patients with hand OA using Kellgren–Lawrence scores.[21]

In this study, the prevalence of PN among patients with RA was 75%. A similar result was found in a study of 89 patients with RA, 75.28% (n = 67) patients had PN electrophysiologically, whereas 20.89% (14 patients of 67) had superficial touch sensory loss on examination. Subclinical neuropathy was present in 50.74% (n = 34) of patients. A statistically significant association between the presence of neuropathy and age of the patients, disease duration, use of disease-modifying anti-rheumatoid drugs, disease severity (disease activity score-28), and presence of subcutaneous nodules (P < 0.05).[14]

In the present study, the prevalence of sudomotor dysfunction among systemic lupus erythematosus (SLE) patients was 80%. Our results is consistent with another study which demonstrated that autonomic nervous system involvement is seen in 93% of the cases of SLE.[22]

In the present study sudomotor dysfunction in AS was 100%, axonal polyneuropathies are reported in 1% to 10% of patients with Sjogren syndrome. These neuropathies are usually symmetric, are sensory or sensorimotor, typically manifest with length-dependent sensory symptoms, have minimal to absent weakness, are insidiously progressive, and rarely require immunosuppressive therapy.[23]

In the present study, sudomotor dysfunction in RD with DM was 75.8%. In a recent study, in T2D, sudomotor dysfunction was found in 66.7% of patients,[24] our higher prevalence may be explained by the presence of RD associated with DM.

Conclusion

PN was prevalent not only among patients with diabetes but also among patients with RDs. Therefore, it is recommended that all patients with RD be routinely screened for PN to detect it early and improve quality of life. The reason of sudomotor dysfunction could be linked to the inflammatory process associated with RD. However, more research is required to determine the exact cause of the high prevalence of autonomic neuropathy among nondiabetic patients with RDs.

Study limitations

This study included a small sample size for some of the RDs such as SLR, RA, and IGG4, conducting the same study in a begger

sample size will be more accurate in assessing the prevalence of neuropathy among RD patients.

Data availability

The corresponding author can provide the datasets utilized and/or analyzed within the current study upon reasonable request.

Acknowledgments and non-author contribution

Appreciate the efforts of the research ethics committee.

Authors' contributions

OM and NMA were responsible for designing the research question, conceptualizing the study, obtaining IRB approvals, formulating the tables, collecting data, performing statistical analysis, interpreting the data, and writing the final manuscript. MI was responsible for data collection, data entry, statistical analysis, and manuscript writing. DS, FI, and MAH were responsible for data collection and manuscript writing. All authors read and approved the final manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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